REMARKS

The Applicants acknowledge the Office Action of January 13, 2004 with appreciation. To begin, the Office raises objections as to form, rejections under 35 U.S.C. § 112 and 35 U.S.C. § § 101, 102 and 103.

The Office objects to Claims 7 and 10 for improper claim dependency. With the Response and Amendment these claims are canceled.

Claims 7-10 are rejected under 35 U.S.C. § 101 for improper definition of a process. Alternatively, Claims 7-10 are rejected under 35 U.S.C. § 112, second paragraph, for improper definition of a process. With the Response and Amendment Claims 7-10 are canceled, thereby obviating the rejections.

Claim 10 is rejected for failing to claim with particularity. Claim 10 is presently canceled.

Claim 11 is also rejected for failing to claim with particularity. The Office is unclear as to what "cosmetic condition" the Applicant is referring. The Applicants direct the Office to the Specificaion, page 8, second paragraph, where disclosure of representative conditions which benefit from cosmetic treatment with the instant invention are enumerated. The Office provides a reference to Benedetto, AV (Intl. J. Dermatol., 1999, 38:641-655) wherein cosmetic indications for Botulinum toxins are disclosed (page 646). The Applicants submit that cosmetic conditions treatable with botulinum neurotoxin are well-known to those skilled in the art as evidenced by the Benedetto disclosure. The instant invention is drawn to the treatment of those cosmetic conditions understood by those skilled in the art to derive benefit from botulinum neurotoxin therapy, with the instant invention being particularly beneficial to individuals who have already developed neutralizing antibodies to neurotoxin

complexes as a result of ongoing treatment of these known cosmetic conditions. It is submitted that those cosmetic conditions that benefit from botulinum neurotoxin therapy are well-known and practiced by one skilled in the art. Therefore, based upon the Specificational disclosure and the understanding of those skilled in the art of neurotoxin therapy, the Applicants submit that the universe of cosmetic conditions treatable with the instant invention is defined and thereby claimed with particularity.

The Office submits that the language "comprising administration of a botulinum toxin" is unclear with regard to whom the toxin is to be administered. The instant invention is drawn to a method of treating a human or animal, as recited in Claim 11. The Applicants submit that there is no ambiguity in the claim language as to whom the botulinum neurotoxin is to be administered. However, to further clarify the subject of administration, Claim 11 is amended to add the language, "comprising administration, to said human or animal, a botulinum neurotoxin..." Similarly, Claim 16 was also amended to include the language, "comprising administration, to said human or animal, a botulinum neurotoxin..." The Applicants submit that the instant amendment provides the requested definition.

Moving on, Claims 7, 10 and 16-18 are rejected under 35 U.S.C. §102(b) as anticipated by Göschel, et al., (Experimental Neurology 1997, 147:96-102). Claims 7 and 10 are canceled. Claims 16-18 are drawn to a method of treating subjects with a purified botulinum neurotoxin and clearly claim the invention in terms of the surprising efficacy in subjects already exhibiting neutralizing antibodies to botulinum neurotoxin complexes. It is understood by those skilled in the art that prolonged treatment with botulinum A toxin results in diminished efficacy due to neutralizing antibody formation against toxin complexes, which is the subject matter of the Göschel, et al. reference. Although Göschel, et al. disclose the use of purified botulinum toxin A, there is no disclosure of the efficacious treatment of subjects already exhibiting neutralizing antibodies to neurotoxin complexes. Furthermore, the reference disclosure suggests that non-responders, which have high titers of

neutralizing antibodies to purified botulinum neurotoxin A, would not benefit from treatment with such a preparation.

Göschel, et al. disclose an assay that utilizes purified botulinum toxin A, admixed with patient serum, to evaluate paralysis of a nerve-muscle preparation. Toxin-specific antibodies in the serum of non-responders neutralize the effect of botulinum toxin A in this assay, which is evidenced by an increased time to paralysis of the nerve-muscle preparation (Figure 3; Table 1). Therefore, it is submitted that Göschel, et al. teach that purified botulinum toxin A would not be effective in subjects who have already generated neutralizing antibodies. As noted by the Office, and in support of the Applicant's assertion, the reference discloses that neutralizing antibodies were the cause of therapeutic failure (page 101). Furthermore, the Office notes that Göschel, et al. teach that "In contrast to patients with neutralizing antibodies, those testing positive for the nonneutralizing antibodies will continue to benefit from the toxin" (page 101). The novelty of the instant invention resides in the discovery that patients exhibiting neutralizing antibodies can be effectively treated with a botulinum neurotoxin free from complexing proteins. Göschel, et al. actually teach away from this surprising discovery. In light of these remarks, reconsideration and withdrawal of the prior art rejection based on the disclosure of Göschel, et al. is respectfully solicited.

It is the Office position that Göschel, et al. teach that a second generation botulinum neurotoxin preparation should be devoid of toxoid and should be purified from concomitant proteins and therefore, anticipates the instant invention. Göschel, et al. discuss potential antigens as sources for neutralizing antibody generation. The reference discloses that the second generation of botulinum toxin preparation should be devoid of toxoid. The toxiod to which Göschel, et al. refer is the tetanus toxiod which shares 35% amino acid homology to botulinum toxin. As disclosed in the reference, immunization against tetanus toxiod potentially generates neutralizing antibodies which are cross-reactive against botulinum toxin. Göschel, et al. teach

that under experimental conditions, neutralizing antibodies against a common epitope have been found. Thus, patients immunized against tetanus toxoid may also be immune to botulinum neurotoxin and thereby are refractive to conventional botulinum toxin therapy. Taken as a whole, Göschel, et al. suggest that neutralizing antibodies, as well as those antibodies which cross-react to neutralize the botulinum neurotoxin are the cause of therapeutic failure. The novelty of the instant invention resides in the discovery that patients exhibiting neutralizing antibodies can be effectively treated with a botulinum neurotoxin free from complexing proteins. The reference disclosure does not suggest that the instant invention may be expected to provide an efficacious treatment for those patients exhibiting neutralizing antibodies and is therefore, not anticipated by the reference disclosure.

Furthermore, the Office submits that Göschel, et al. teach that a second generation botulinum neurotoxin preparation should be purified from concomitant proteins. The Applicants submit that Göschel, et al. teach that the concomitant proteins contribute to nonneutralizing antibody generation and may also serve as adjuvants that stimulate the production of anti-neurotoxin antibodies (page 102). The reference discloses that elimination of concomitant proteins will reduce the load of foreign substances that lead to undesired immune system stimumlation. Therefore, antibody generation may be expected to be reduced and adverse side effects, such as untoward reactions, may be expected to be diminished. The Applicants submit that the second generation toxin being free from concomitant proteins, as disclosed in Göschel, et al., relates to a divergent process which is the reduction of the development of neutralizing antibodies. The reference disclosure does not anticipate, nor suggest that a second generation toxin free from complexing proteins would be efficacious in the treatment of subjects that already exhibit neutralizing antibodies.

The instant invention is drawn to a method of treating individuals who already exhibit neutralizing antibodies. The novelty of the instant invention resides in the rapid

bioavailability of the purified botulinum neurotoxin and the discovery that patients exhibiting neutralizing antibodies can be effectively treated with a botulinum neurotoxin free from complexing proteins. Göschel, et al. does not anticipate, nor suggest this surprising activity. Additionally, Göschel, et al. is silent on the use of other types of purified botulinum toxins, alone or as a mixture, as an effective therapy for patients exhibiting neutralizing antibodies. These distinguishing features are not anticipated by the reference disclosure. Reconsideration and withdrawal of the prior art rejection based on the disclosure of Göschel, et al. is respectfully solicited.

Claims 8 and 9 are rejected under 35 U.S.C. § 102(b) as anticipated by Keen et al., (Plastic and Reconstructive Surgery, July 1994, 94(1):94-99). Claims 8 and 9 are also rejected under 35 U.S.C. § 102(b) as anticipated by Shelley et al., (J Am Acad Dermatol. 1998, 28:227-9). With the Response, Claims 8 and 9 are canceled, thereby obviating the rejections.

Moving on, Claims 7-13 and 16-18 are rejected under 35 U.S.C. § 103(a) as unpatentable over Göschel, et al. in view of Shelley, et al. The Office submits that it would be *prima facie* obvious to treat patients having hyperhidrosis, as in Shelley, et al., with botulinum toxin A, wherein the patient exhibits neutralizing antibodies. The Applicants rely on the teaching of Göschel, et al. wherein patients treated unsuccessfully with botulinum toxin A, have developed neutralizing antibodies and, therefore, are refractive to therapy. Göschel, et al. disclose a sensitive in vitro toxin-neutralizing assay to discriminate neutralizing antibodies in the sera of patients. The presence of neutralizing antibodies in the serum of non-responders is evidenced by an increased time to paralysis of the nerve-muscle preparation (Figure 3; Table 1). The antibodies present in the serum of non-responders neutralize the effect of botulinum toxin A. Göschel, et al. disclose that the presence of neutralizing antibodies is the cause of therapeutic failure (page 101). Therefore, it is not obvious from Göschel, et al. that a purified botulinum toxin preparation would provide benefit

to humans or animals exhibiting neutralizing antibodies to neurotoxin complexes. Furthermore, the Applicants submit that the reference disclosure suggests that purified botulinum toxin A would not have such benefit. The Applicants submit that in Göschel, et al. there is no reasonable expectation of success for the treatment of subjects exhibiting neutralizing antibodies and therefore, no motivation to combine the teachings of Shelley, et al. Consequently, the instant rejection for anticipation and/or obviousness is not supported by the art of record.

The Office rejects Claims 7-12 and 14-18 under 35 U.S.C. 103 (a) as unpatentable over Göschel, et al. in view of Keen, et al. The Office submits that it would be *prima facie* obvious to treat patients having facial wrinkling, as in Keen, et al. with botulinum toxin A, wherein the patient exhibits neutralizing antibodies. Again, the Applicants rely on the teaching of Göschel, et al. wherein the presence of neutralizing antibodies in non-responders reduces the efficacy of botulinum toxin A in a toxin-neutralizing assay. There is no reasonable expectation that the instant invention would be efficacious in subjects exhibiting neutralizing antibodies and therefore, there is no motivation to combine the teachings of Keen, et al. The unobviousness of the instant invention lies in the surprising result that non-responders can benefit from treatment with the instant invention. In light of these remarks, we submit the Office has not established *prima facie* obviousness.

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Accordingly, entry of the amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of

assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,
THE FIRM OF HUESCHEN AND SAGE

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